UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/420,433	10/12/99	SIDRANSKY D	JHU1180-1

HM22/0307

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EXAMINER	
JOHANNSEN, D	
ART UNIT	**PAPER NUMBER**
1655	8

DATE MAILED: 03/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/420,433	Sidransky
Examiner	**Group Art Unit**
Diana Johannsen	1655

☒ Responsive to communication(s) filed on *Jan 10, 2001*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

FINAL ACTION

1. This action is in response to paper no. 6 filed December 21, 2000. Claims 1-12 and 17-18 have been amended, and claims 1-18 are pending. The amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims.

This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 U.S.C. § 112

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

3. Claims 2-3 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-3 and 11 are indefinite because is it unclear as to how the claims are intended to further limit the claims from which they depend. Claim 2 as amending requires "The method of claim 1, further comprising amplifying the nucleic acid present in the specimen to produce an amplified nucleic acid before detecting the presence of the mutant target nucleic acid in the amplified nucleic acid". The claim does not make clear how the steps of claim 2 relate to the

steps of claim 1, and particular to the "detecting" step of claim 1. For example, are the steps of claim 2 to be performed in addition to or instead of the "detecting" step of claim 1, and how does detection of "the presence of the mutant target nucleic acid in the amplified nucleic acid" relate to "detecting the presence of a mammalian mutant target nucleic acid", as required by the preamble of claim 1? Clarification is required with respect to how claim 2 and the claims dependent therefrom are intended to further limit claim 1.

Claim Rejections - 35 U.S.C. § 102

4. In view of the amendment of independent claims 1, 12, and 18 to require detection of a "mutant target sequence" (claim 1) or a nucleic acid "having a mutant nucleotide sequence" (claims 12 and 18), the rejection of claims 1-3, 5, 10, 12-14, and 17-18 under 35 U.S.C. 102(e) as being anticipated by Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]) is withdrawn.

Claim Rejections - 35 U.S.C. § 103

5. In view of the amendment of claim 1 to require detection of a "mutant target sequence", the rejection of claims 7-9 under 35 U.S.C. 103(a) as being unpatentable over Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]) in view of McAnalley et al (U.S. Patent No. 5,587,364 [12/24/1996; effective filing date 7/27/1990) is withdrawn.

6. In view of the amendment of claim 1 to require detection of a "mutant target sequence", the rejection of claim 11 under 35 U.S.C. 103(a) as being unpatentable over Sobol et al in view of Mullis et al (U.S. Patent No. 4,683,195 [7/28/1987]) is withdrawn.

7. Claims 1-6, 10, and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]) in view of Effert et al (J. Urology 147:789-793 [2/1992]), for the reasons stated below and in the Office action of paper no. 4. **It is noted that applicant's amendments to the claims necessitated the inclusion of claims 1-3, 5, 10, 12-14, and 17-18 in this rejection.**

Sobol et al teach methods for detecting carcinoma metastases comprising extraction of nucleic acids from a sample of tissue or fluid and detection of a "carcinoma associated sequence" (see entire reference). The samples analyzed by Sobol et al's methods may include both fluids and tissues, including lymph nodes (see, e.g., col 4, lines 52-59). Sobol et al teach that conventional diagnostic methods may fail to detect residual or metastatic disease, and disclose that their methods are more sensitive than convention methods, including histological analysis (see, e.g., col 2, lines 13-52; col 4, lines 33-35; col 5, lines 28-35). Sobol et al teach a variety of targets that may be analyzed by their methods, but do not specifically teach or suggest employing their methods to detect a "mutant target nucleic acid" or a nucleic acid "having a mutant nucleotide sequence". Further, with respect to claims 4, 6, and 15-16, Sobol et al do not teach or suggest employing their methods to detect a "mutated tumor suppressor" or targets containing a mutation "selected from the group consisting of a restriction fragment length polymorphism, a nucleic acid

deletion, and a nucleic acid substitution", or teach or suggest detection of p53 or the other tumor suppressors recited in claim 6. Effert et al disclose that p53 mutations, which are "most commonly single point mutations", may be detected both in primary tumor samples and in samples from sites of metastasis, including lymph nodes (see entire reference). In view of the teachings of Effert et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Sobol et al so as to have detected p53 mutations in histologically normal lymph node tissues from prostate carcinoma patients. Effert et al disclose that mutations present at metastatic sites, particularly lymph nodes, may play a role in "the progression of human prostate cancer" (p. 789), and Sobol et al disclose that their amplification based detection methods may be employed to detect metastasis in tissues that appear normal by histological analyses. Accordingly, an ordinary artisan would have been motivated to have so modified the method of Sobol et al for the advantage of achieving early, rapid and sensitive detection of carcinoma metastasis. With further respect to claims 2-3, it is noted that Sobol et al's methods comprise amplification with oligonucleotides that flank a target sequence (see entire reference, especially col 4, lines 4-8). With respect to claim 4, it is noted that the single point mutations taught by Effert et al constitute nucleic acid substitutions. With respect, to claims 5, 15, and 17, it is noted that the combined teachings of Sobol et al and Effert et al are sufficient to suggest detection of cancer-associated mutations in oncogenes and/or tumor suppressors. With respect to claim 13, Sobol et al disclose that PCR is sufficiently sensitive to detect a target nucleic acid present in only 1 of 10,000 cells (col 2, lines 46-52). With respect to

claim 14, Sobol et al disclose that their methods are sufficiently sensitive to detect targets in histologically normal tissue (see, e.g., col 2, lines 13-52; col 4, lines 33-35; col 5, lines 28-35). With respect to claim 18, it is a property of the sample types disclosed by Sobol et al and Effert et al that they are "external to a primary neoplasm".

With respect to the rejection of claims 4, 6, and 15-16 as being unpatentable over Sobol et al in view of Effert et al in the Office action of paper no. 4, the response traverses the rejection on the following grounds. The response argues that "there is nothing in the Sobol et al. reference relating to the detection of mutant nucleic acid sequences such as a mutant p53 nucleic acid". The response states that "the basis of the Sobol et al. reference is that metastases are identified by the expression of an otherwise normal gene product in an abnormal location" and that "Sobol et al. specifically indicate that '[i]n contrast to prior methods for cancer detection, the target nucleic acid is not necessarily an oncogene mRNA product'". The response argues that "absent Applicants' disclosure, one of ordinary skill in the art would not have been motivated to use the method of Sobol et al. to detect a mutant nucleic acid as suggested by Effert et al. because Sobol et al. specifically disclose the detection of otherwise normal gene products "in contrast to prior methods for cancer detection".

These arguments have been thoroughly considered but are not convincing for the following reasons. While it is acknowledged that Sobol et al indicate that their method is an improvement of prior art methods in that it can be used to detect "expression of an otherwise normal gene product in an abnormal location", as the response states, Sobol et al's statement that

"the target nucleic acid is not necessarily an oncogene mRNA product'" clearly indicates that their method provides an improvement in that it may be used in detection of both oncogenic and non-oncogenic products. The statement "is not necessarily an oncogene" suggests that while Sobol et al's method is applicable to detection of non-oncogenic products, including abnormally expressed gene products, it would also be applicable to detection of other cancer-associated products disclosed in the art, including oncogenes. Further, while it is acknowledged that Sobol et al do not teach a "mutant p53 nucleic acid", as asserted by the response, the Effert et al reference was cited for its teaching of such nucleic acids. Given Sobol et al's suggestion that their method would be applicable to a variety of cancer-associated targets, and Sobol et al's disclosure, e.g., that "The sensitivity of the present methods distinguish the invention from prior methods for detecting metastasized tumor cells", an ordinary artisan would therefore have been motivated to have modified the invention of Sobol et al so as to have detected "mutant" p53 nucleic acids or other cancer-associated mutant nucleic acids known in the art in histologically normal tissues for the advantage of achieving early, rapid and sensitive detection of tumor metastasis, as suggested by Sobol et al, and as discussed above and in the Office action of paper no. 4.

The combined references of Sobol et al and Effert et al suggest all the limitations of present claims 1-6, 10, and 12-18, and therefore this rejection is maintained.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

8. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al in view of Effert et al, as applied to claims 1-6, 10, and 12-18, above, and further in view of McAnalley et al (U.S. Patent No. 5,587,364 [12/24/1996; effective filing date 7/27/1990).

The combined references of Sobol et al and Effert et al do not teach or suggest detecting "mutant target" nucleic acids that "contribute to the etiology" of benign neoplasms or head or neck tumors, as required by instant claims 7-9. McAnalley et al disclose a variety of tumor types that cause disease in animals, including benign neoplasms and malignant tumors of the head and neck (col 16, line 43-col 17, line 5). In view of the teachings of McAnalley et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Sobol et al in view of Effert et al so as to have detected "mutant" nucleic acid targets associated with benign neoplasms and/or head and neck tumors, as well as other tumor types, in samples from regional lymph nodes and/or tumor margins. An ordinary artisan would have been motivated to have made such a modification for the advantage of achieving early, rapid, and sensitive detection of tumor transformation and/or metastasis.

9. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al in view of Effert et al, as applied to claims 1-6, 10, and 12-18, above, and further in view of Mullis et al (U.S. Patent No. 4,683,195 [7/28/1987]).

The combined references of Sobol et al and Effert et al do not teach or suggest a step of cloning amplified target sequences prior to detection. Mullis et al disclose that the cloning of amplification products allows one to rapidly sequence or express a target molecule of interest

(see, e.g., col 15, line 16-col 16, line 13). In view of the teachings of Mullis et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Sobol et al in view of Effert et al so as to have cloned amplification products comprising "carcinoma associated sequences". An ordinary artisan would have been motivated to have made such a modification in order to have, for example, sequenced such products for the advantage of confirming the sequence of a target nucleic acid detected at a metastatic site, or for the advantage of rapidly detecting the presence of additional novel mutations in such a sequence.

Double Patenting

10. Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,025,127. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons stated in the Office action of paper no. 4. The response does not traverse the rejection. The instant claims as amended remain sufficiently broad so as to encompass the '127 claims, and it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the '127 claims so as to have eliminated some of the limitations of the '127 claims (e.g., the requirement for particular oligonucleotides) so as to have arrived at the instant claims. An ordinary artisan would have been motivated to make such a modification for the advantage of, e.g., increasing the number of different tumor types that could be detected by

the claimed method. Accordingly , the instant claims and the '127 claims are not patentably distinct from each other. This rejection is maintained.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday from 7:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at 703/308-1152. The fax phone number for the

Technology Center where this application or proceeding is assigned is 703/305-3014 or 305-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana Johannsen

March 7, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

3/7/01